

Replacement Sheet

Replacement Sheet

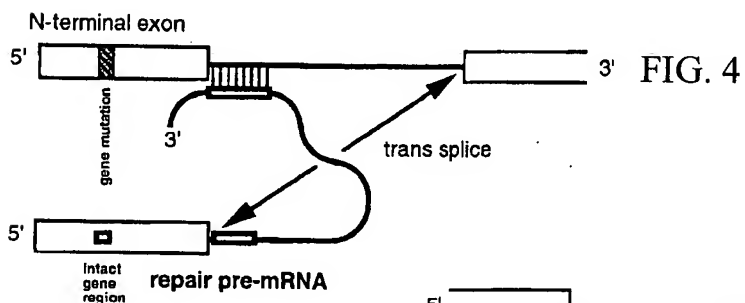
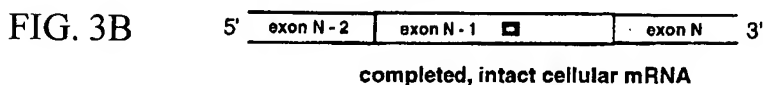
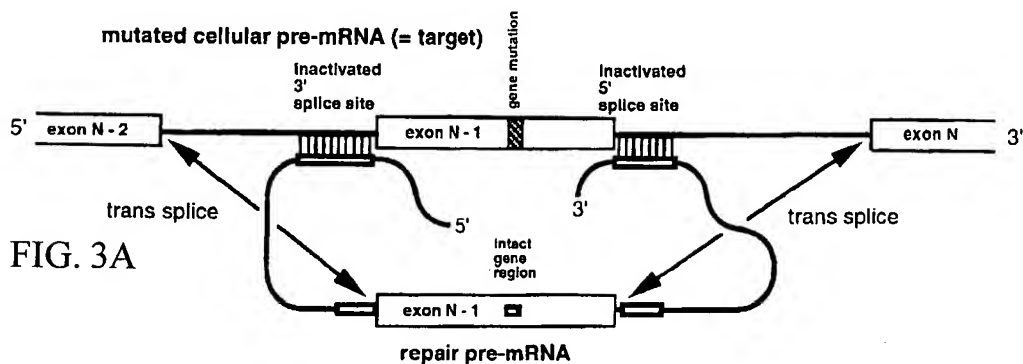
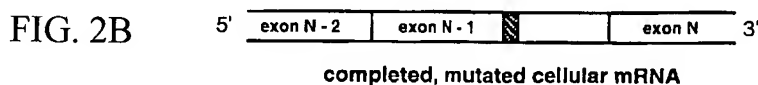
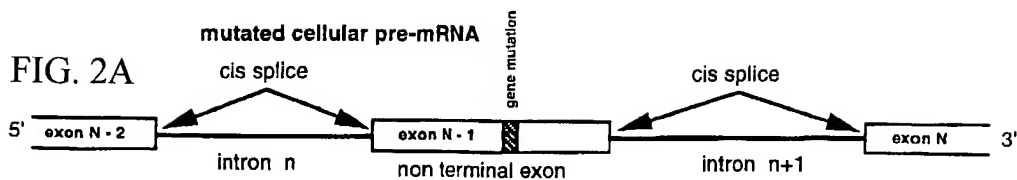
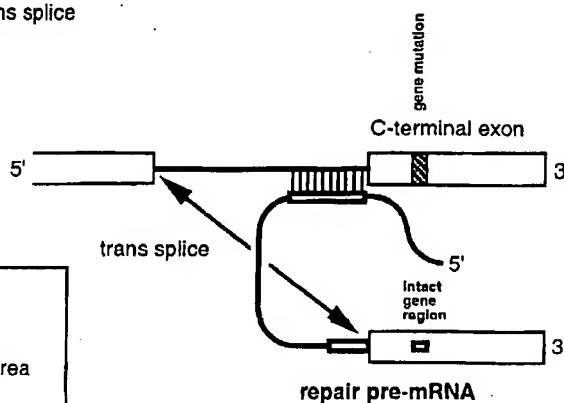
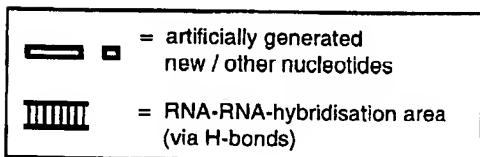
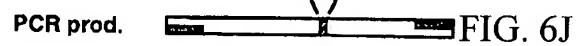
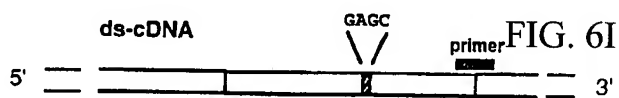
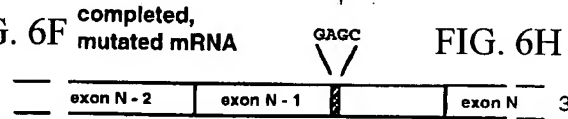
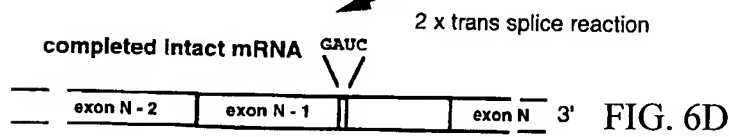
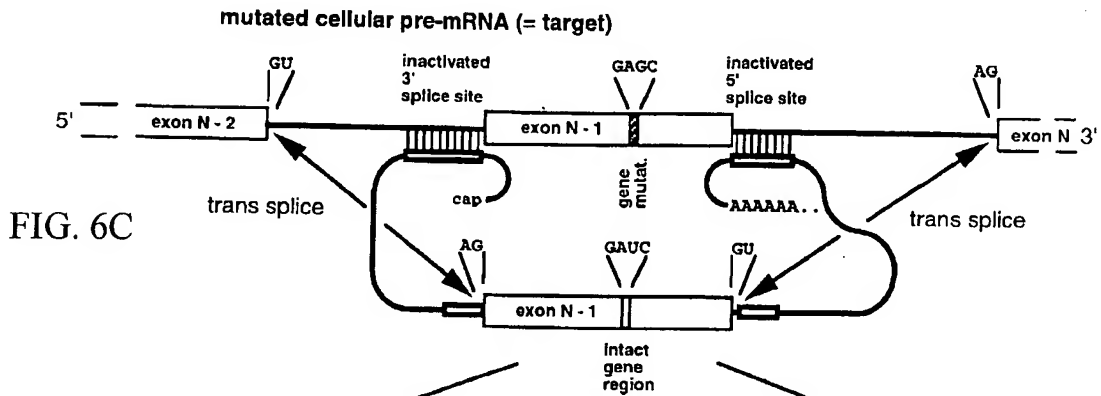
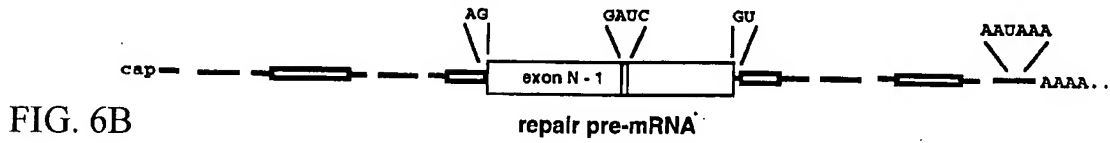
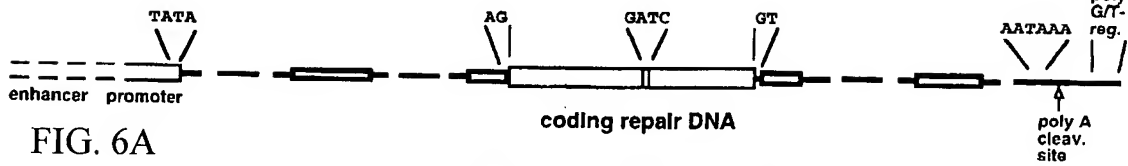


FIG. 5



repair of internal, N- or C-terminal gene mutated exons by trans splicing

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identification of repaired (intact)
and not repaired (mutated) mRNA

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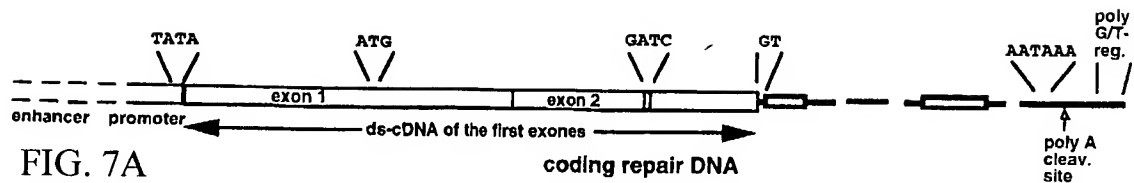
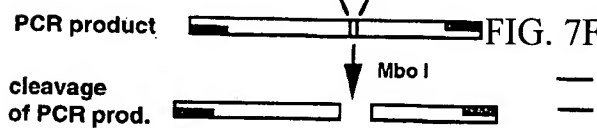
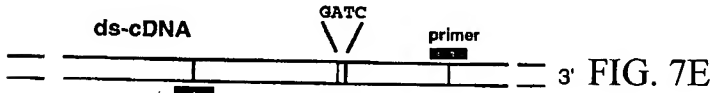
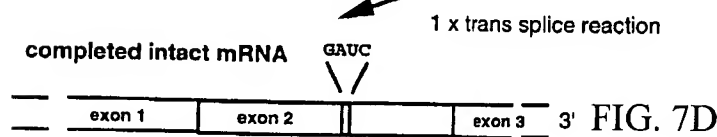
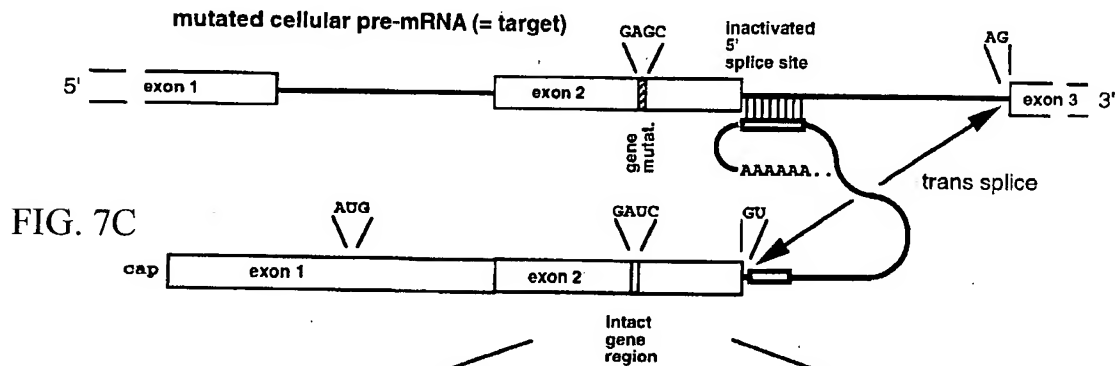
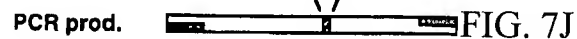
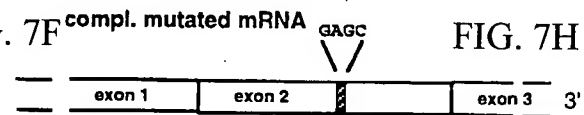


FIG. 7B repair pre-mRNA (with the first exons) and with a potent 5' splice site



identification of repaired (intact) and not repaired (mutated) mRNA



Replacement Sheet

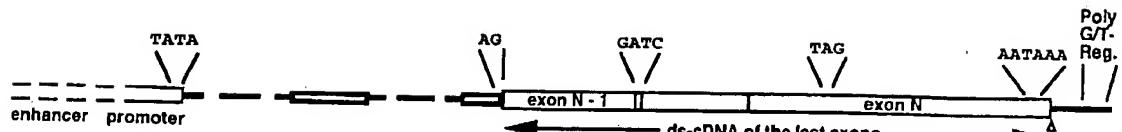


FIG. 8A

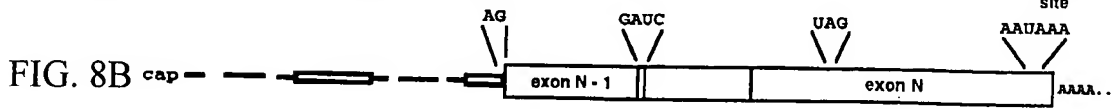


FIG. 8B

repair pre-mRNA (with the last exons)
and with a potent 3' splice site

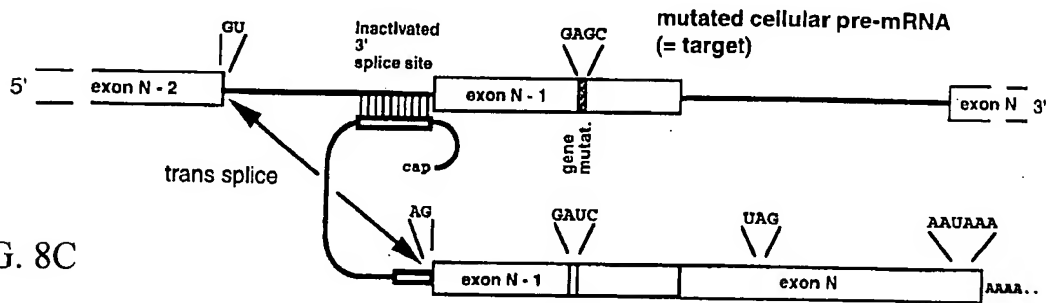


FIG. 8C

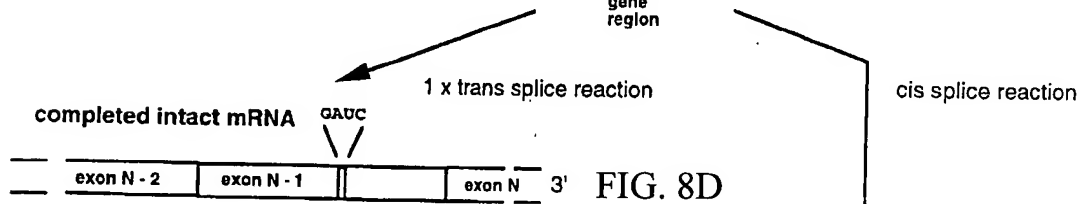


FIG. 8D

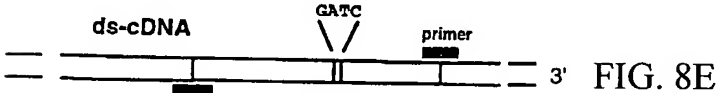


FIG. 8E

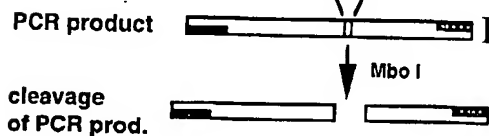


FIG. 8G

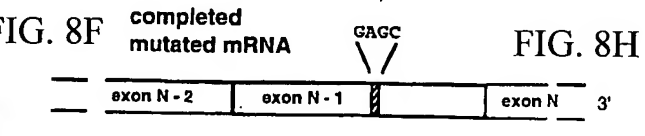


FIG. 8H

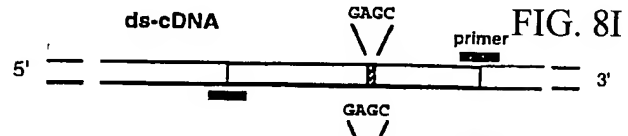


FIG. 8I

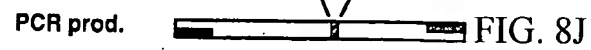


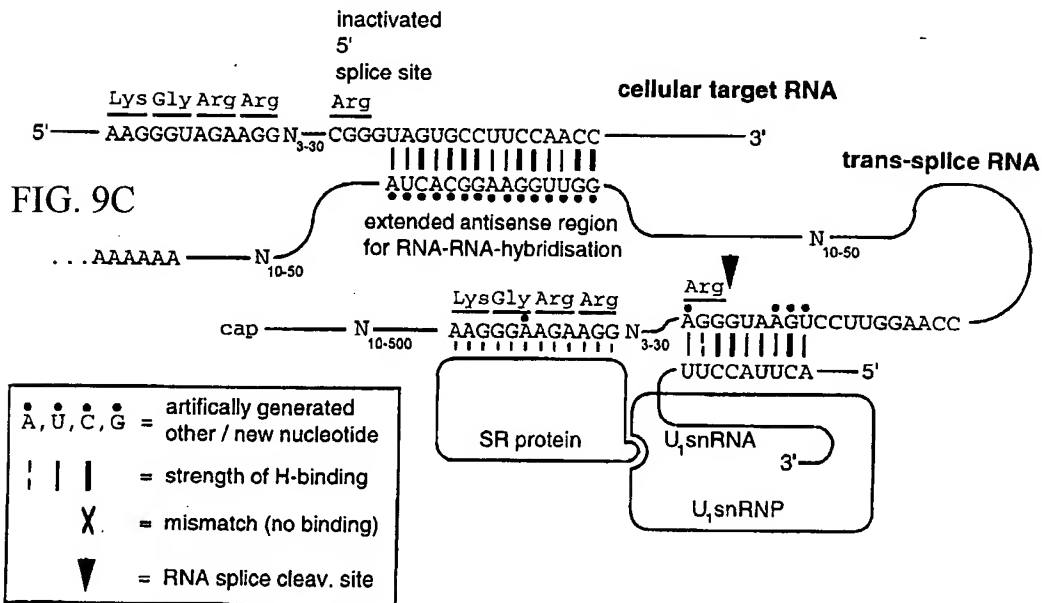
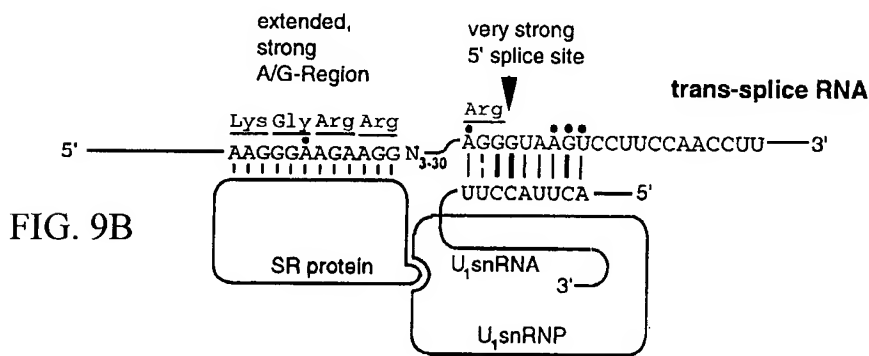
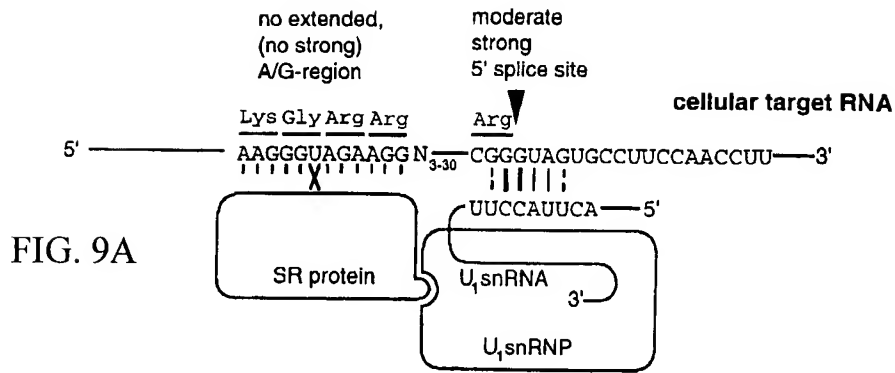
FIG. 8J



FIG. 8K

identification of repaired (intact)
and not repaired (mutated) mRNA

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methodes to prefer the use of a 5' splice site on a trans-splice RNA

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FIG. 10A

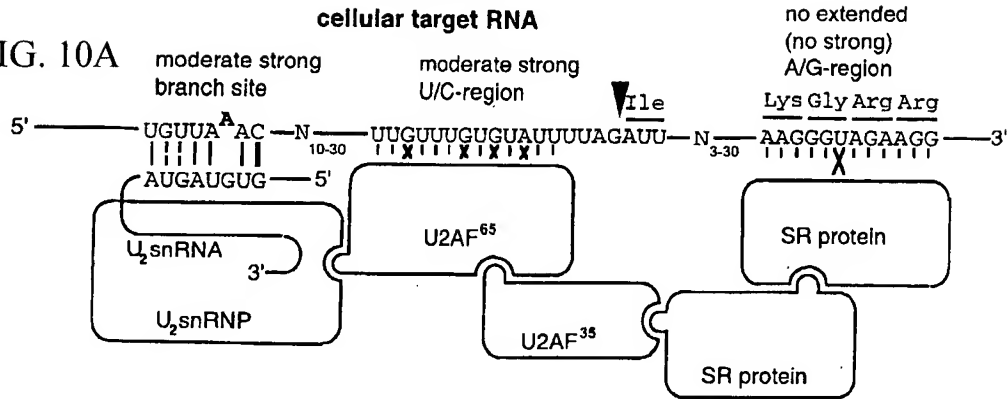


FIG. 10B

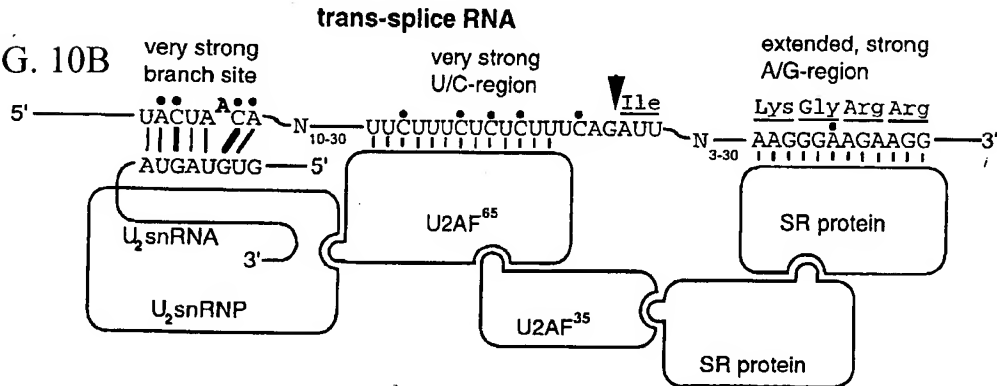
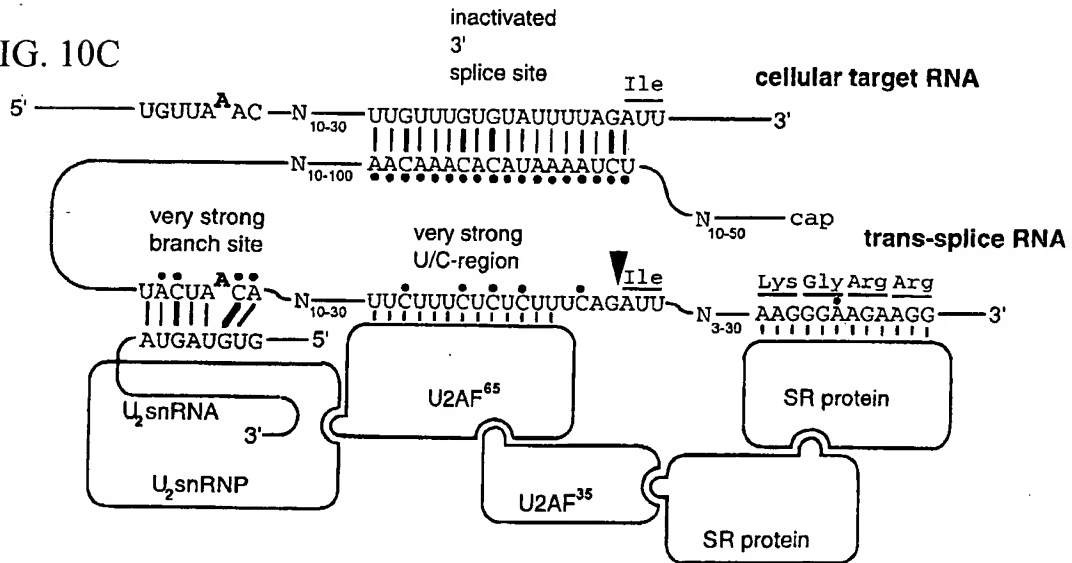
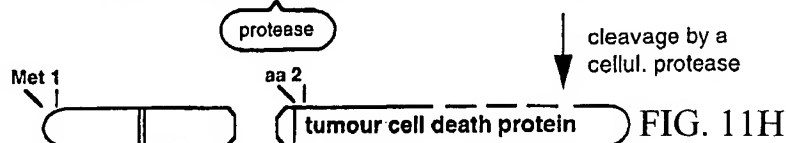
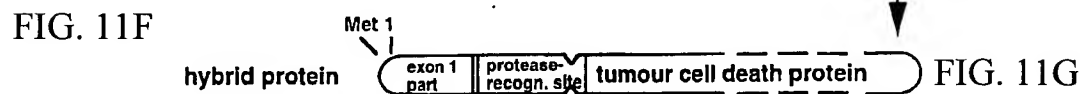
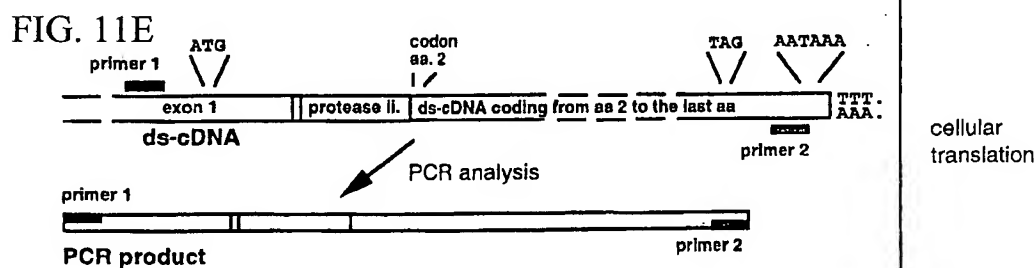
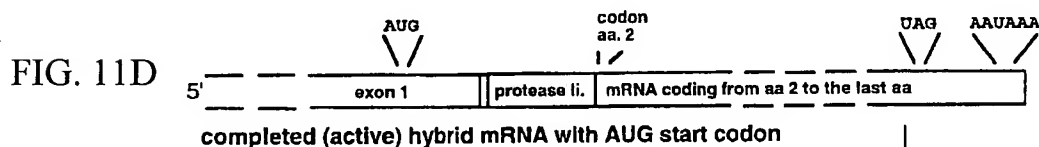
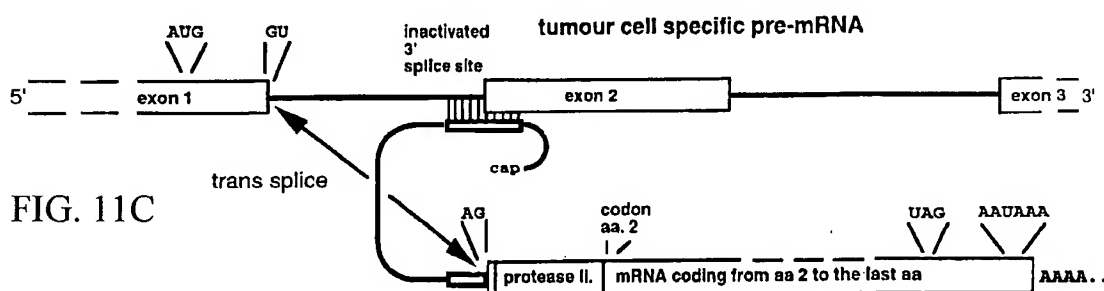
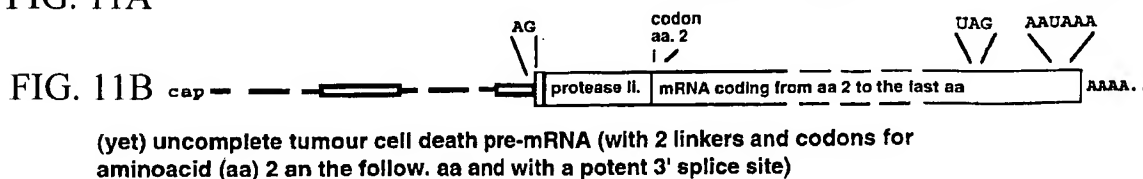
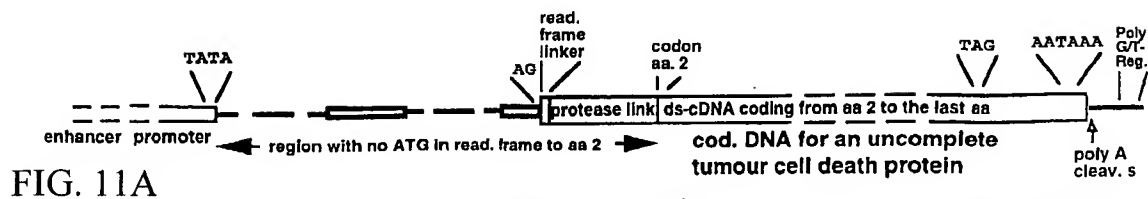


FIG. 10C



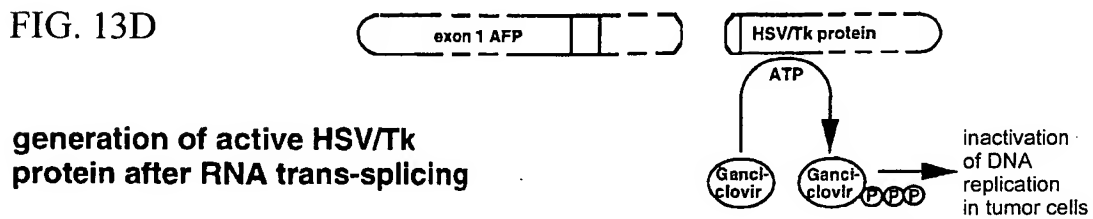
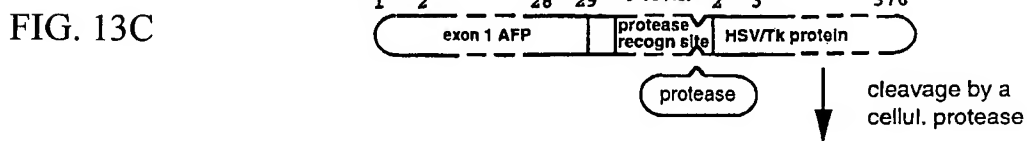
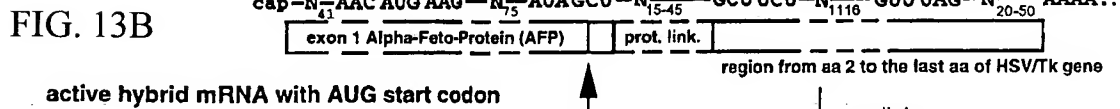
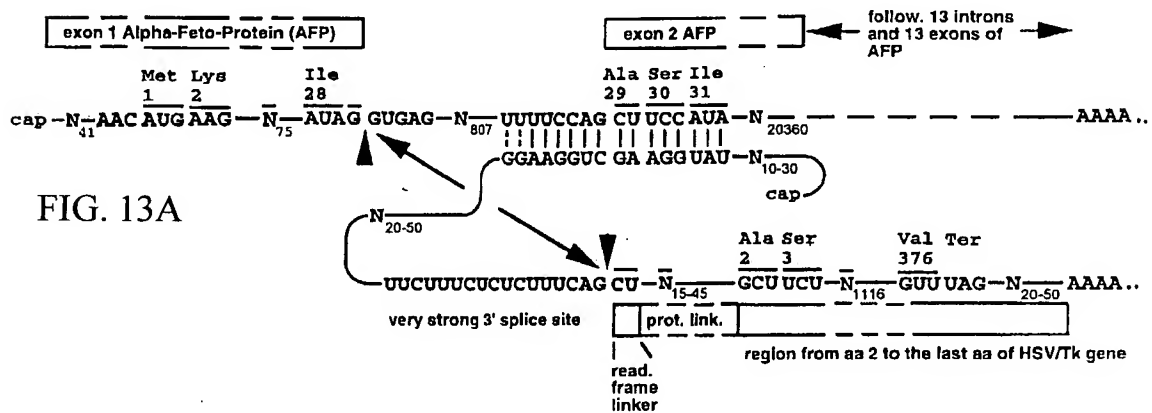
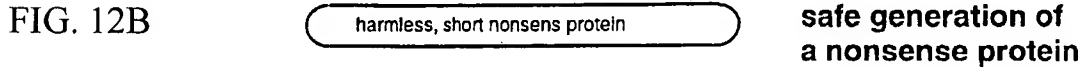
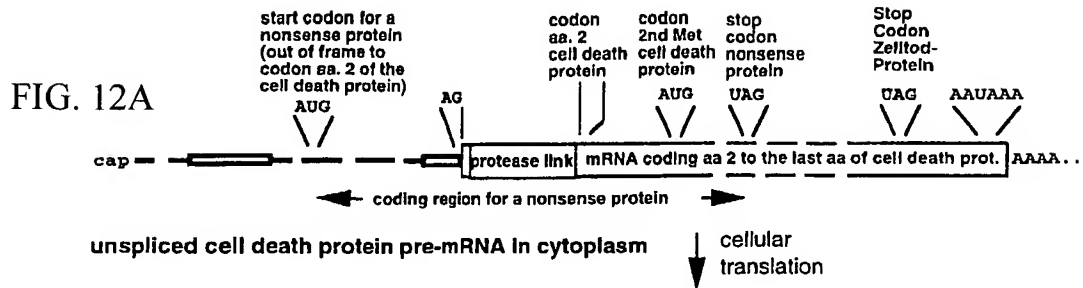
methodes to prefer the use of a 3' splice site on a trans-splice RNA

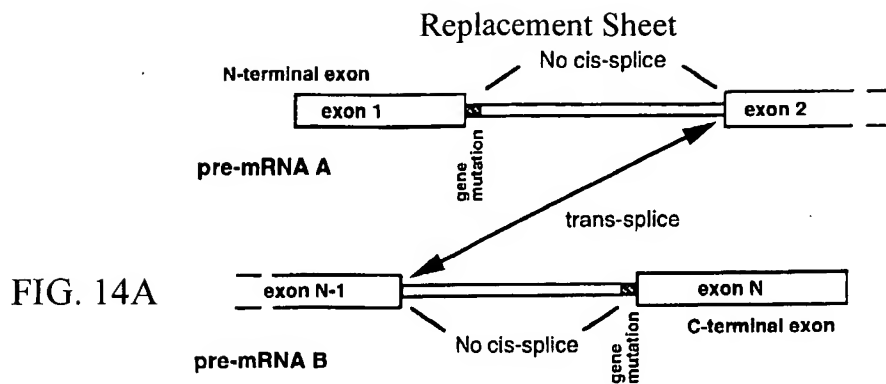
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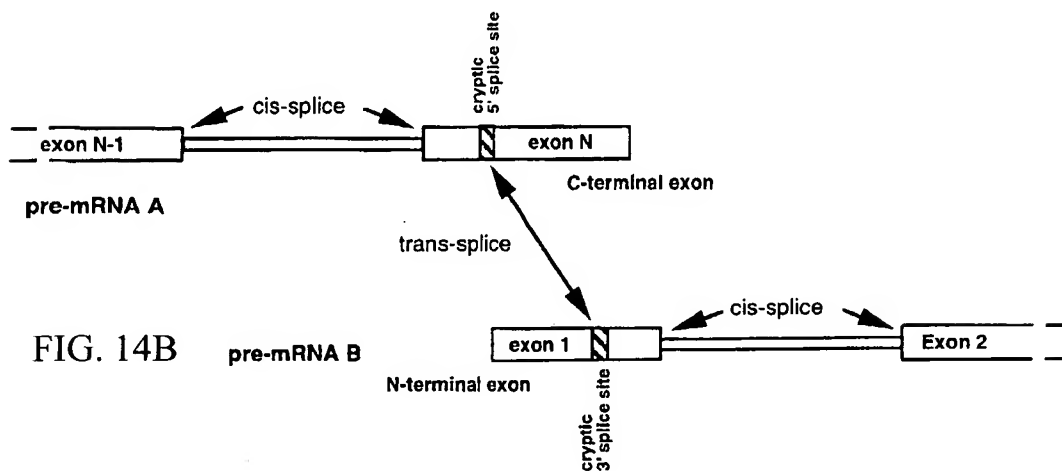
generation of deadly proteins in tumour cells after trans splicing

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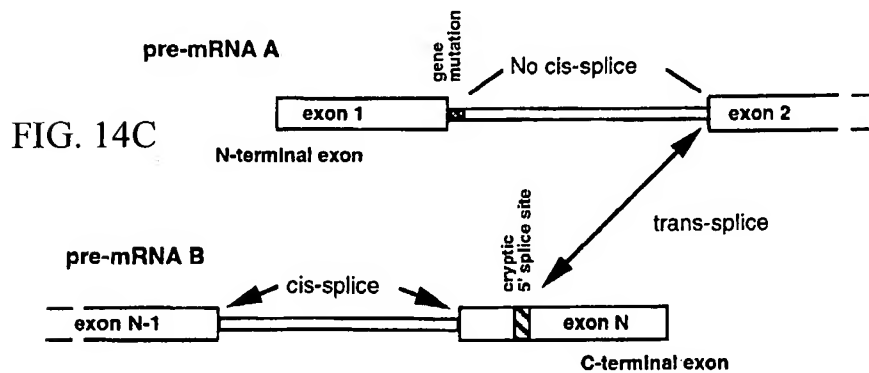




**stimulation of trans-splicing
by mutations in the cis splice sites in N- or C-terminal introns**



**stimulation of trans-splicing
by activating cryptic splice sites in N- or C-terminal exons**



**stimulation of trans-splicing by activating a cryptic splice site in N- or
C-terminal exon and a mutation in a cis-splice site in a N-terminal intron**

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FIG. 15A

step 1: identification potential pre-mRNAs for RNA trans-splicing

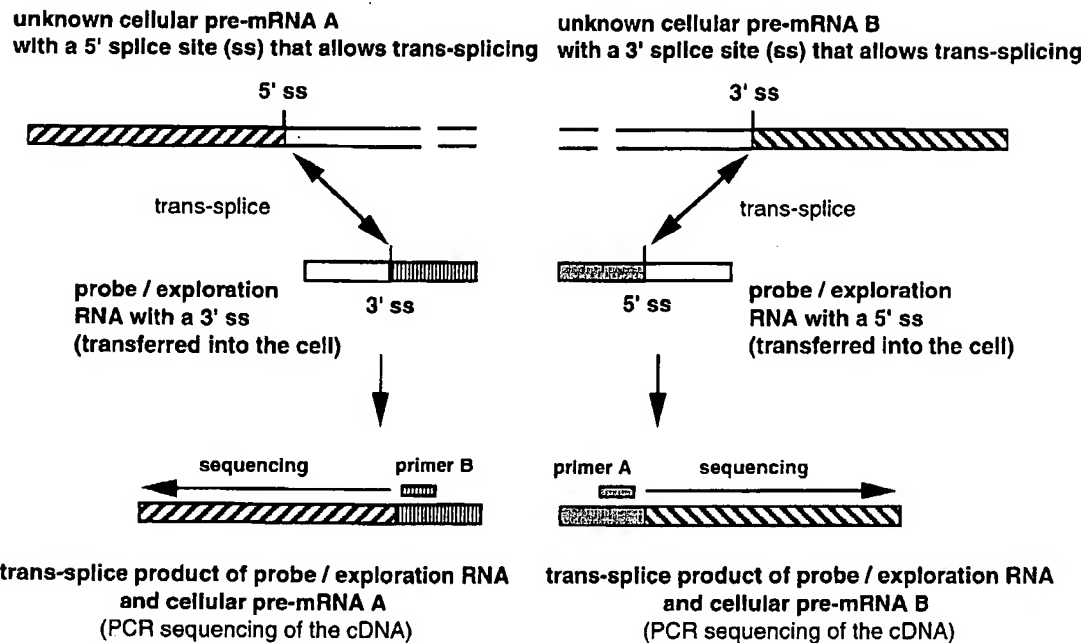
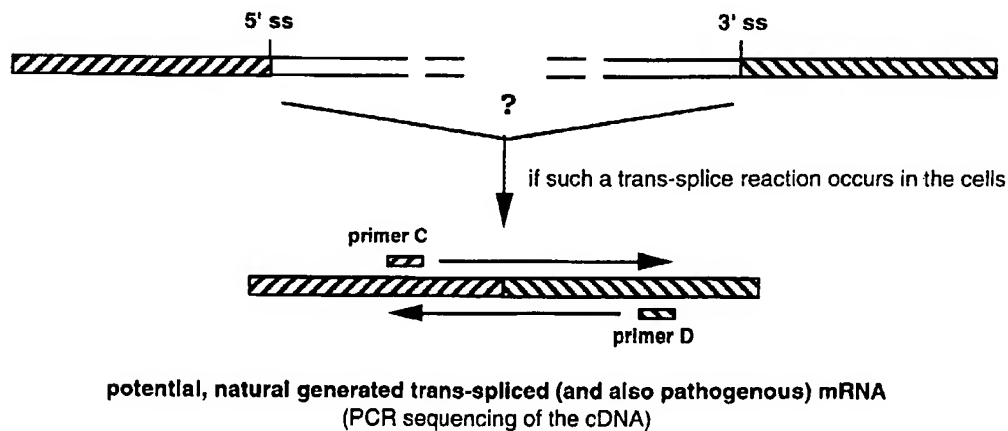


FIG. 15B

step 2: identification of potential natural cellular trans-splice products



principle of identification of yet unknown cellular mRNA trans-splice products

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**unknown cellular pre-mRNA
with a 5' splice site (ss) that allows trans-splicing**

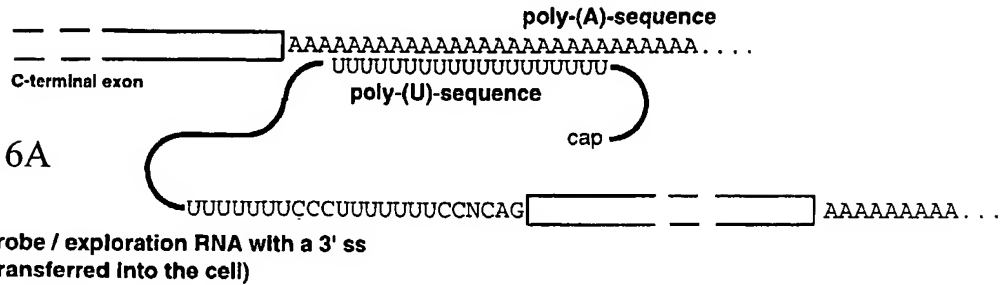


FIG. 16A

association between a probe / exploration RNA and a cellular pre-mRNA that allows trans-splng by antisense pairing between a poly-U-region on the probe / exploration RNA and the poly-A-tail-region on the cellular pre-mRNA

unknown pre-mRNA
with a (cryptic) splice site that allows trans-splicing and bound U₄snRNP

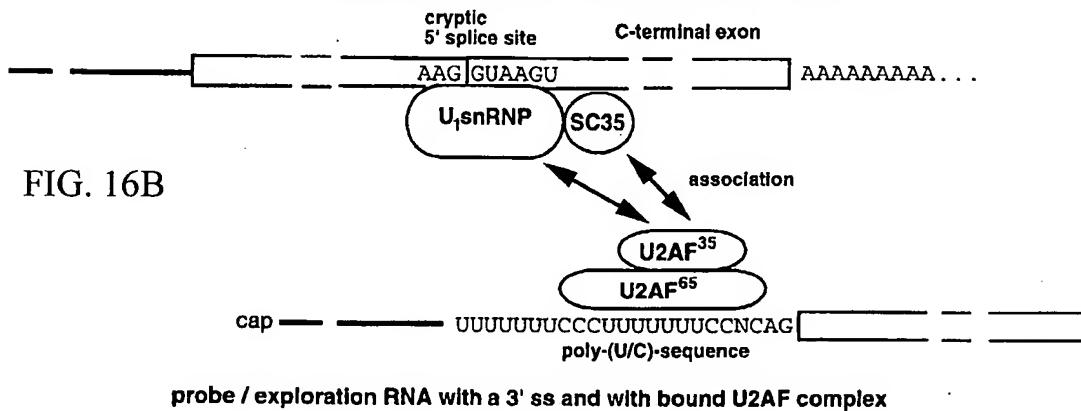


FIG. 16B

association of the 3' splice site on a probe / exploration RNA
to a cryptic 5' splice site in a cellular pre-mRNA that allows trans-splicing
by previously bound splice proteins in the E-complex

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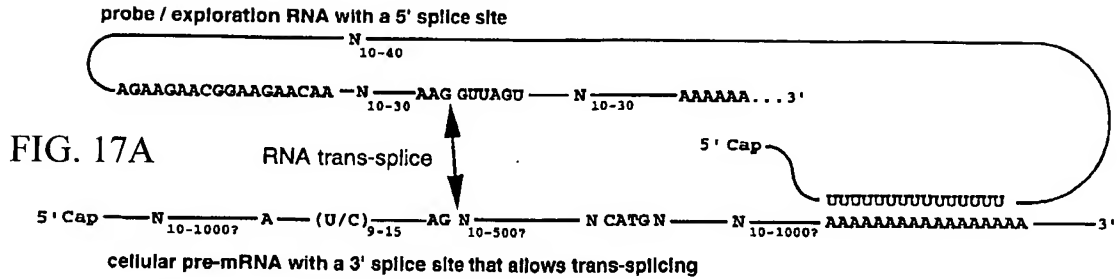


FIG. 17A

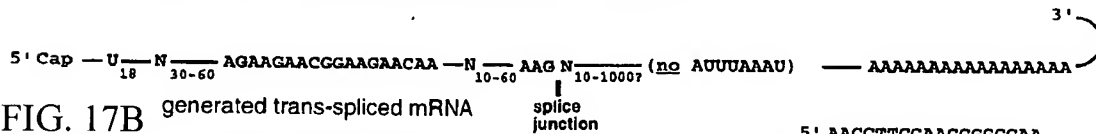


FIG. 17B

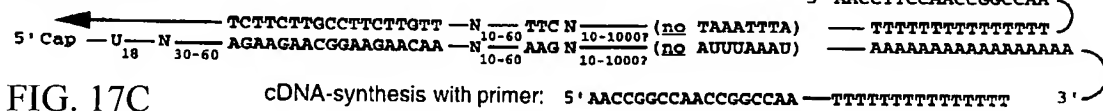


FIG. 17C



FIG. 17D

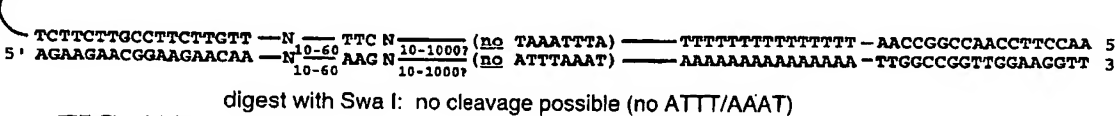


FIG. 17E



FIG. 17F



FIG. 17G

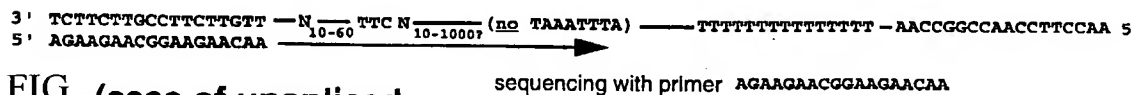


FIG. 17H (case of unspliced probe / explorat. RNA)

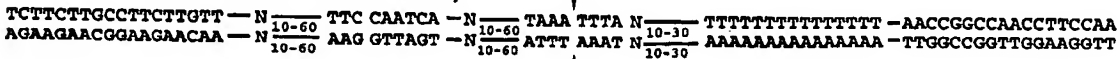


FIG. 17I

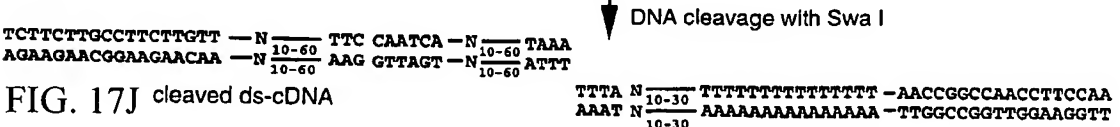
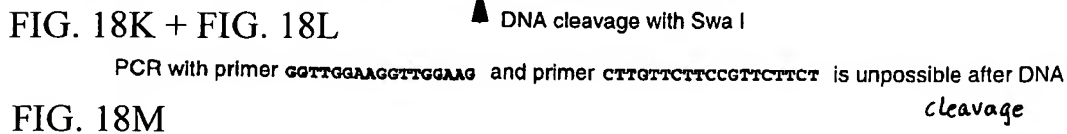
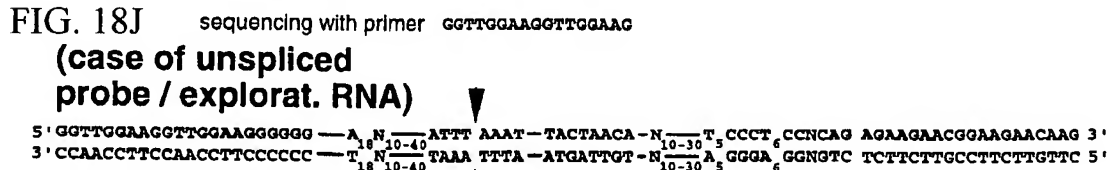
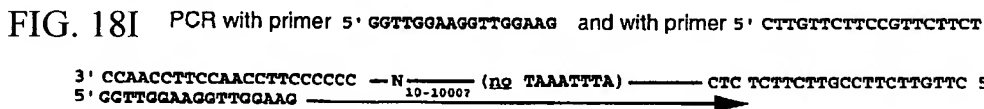
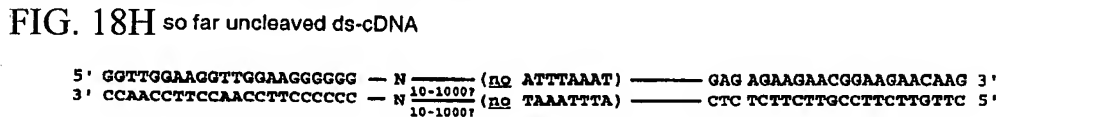
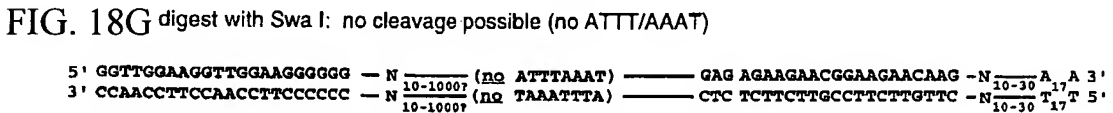
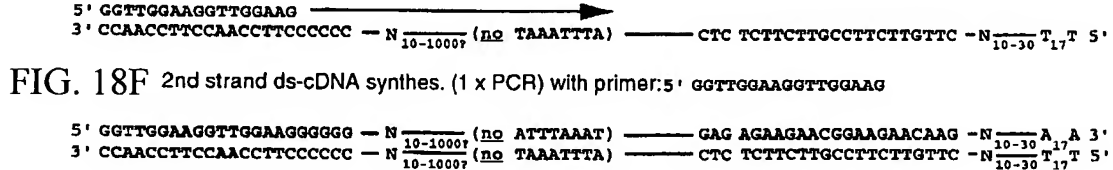
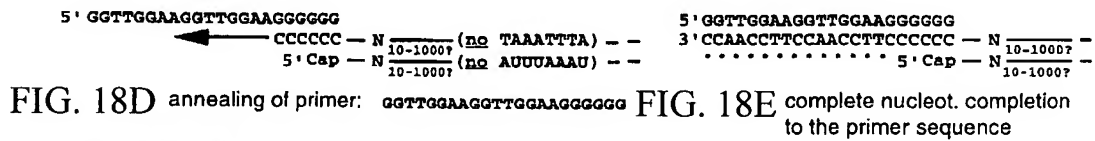
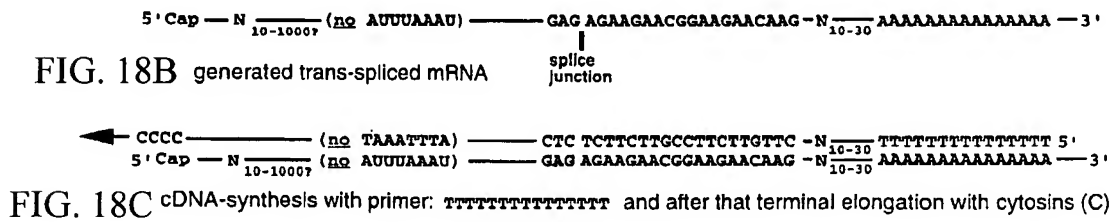
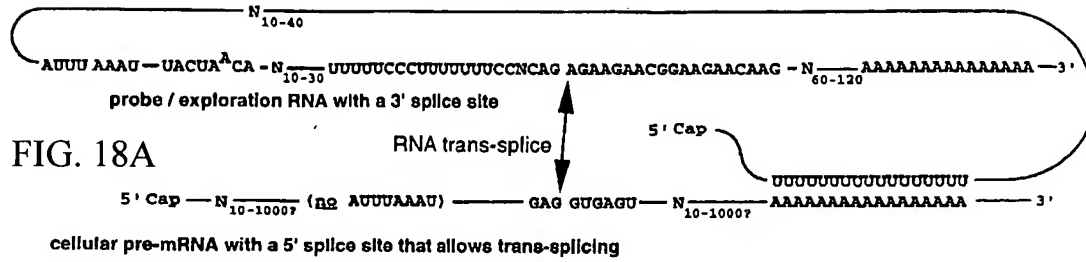


FIG. 17J cleaved ds-cDNA

FIG. 17K PCR with primer AGAAGAACGGAAGAACAA and primer AACCTTCCAACCGGCCAA is impossible after DNA cleavage

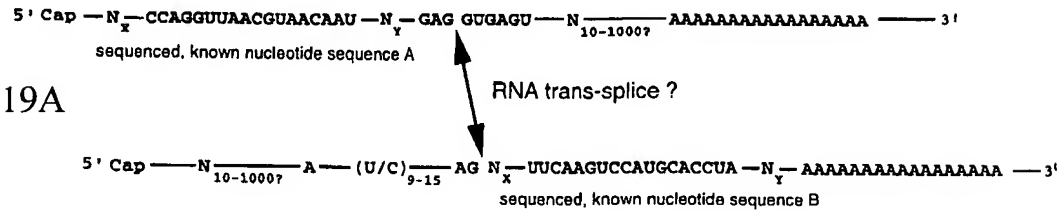
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cellular pre-mRNA A with a 5' splice site that allows trans-splicing

FIG. 19A



cellular pre-mRNA A with a 3' splice site that allows trans-splicing

FIG. 19B

if RNA trans-splice occurs in vivo: generated cellular hybrid mRNA

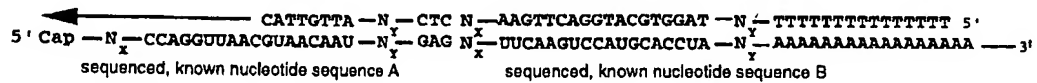


FIG. 19C cDNA synthesis with primer TTTTTTTTTTTTTT

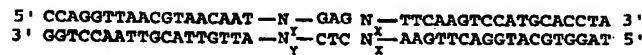


FIG. 19D

PCR with primer 5' CCAGGTTAACGTAACAAT and primer 5' TAGGTGCATGGACTTGAA

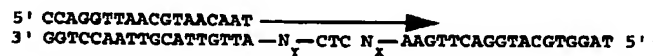


FIG. 19E

confirming sequencing with primer CCAGGTTAACGTAACAAT

final evidence on natural cellular trans-splice products
generated by trans-splicing between two pre-mRNAs that both allow trans-splicing